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PATHOGENESIS OF INFECTIONS OF THE ADRENAL GLAND LEADING TO ADDISON'S DISEASE IN MAN: THE ROLE OF CORTICOIDS IN ADRENAL AND GENERALIZED INFECTION

By

J. K. FRENKEL

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Addison[1] described the syndrome of primary adrenocortical insufficiency in patients the majority of whom had tuberculosis. He recognized the relationship between infection and destruction of the gland and described the clinical picture and the gross appearance of the lesions. This was later elaborated by others with clinical, biochemical, and histologic studies.[2,3] Why tubercle bacilli could infect and so completely destroy both adrenal glands has been obscure. Curiously, there is little in the literature concerning the possible pathogenesis of tuberculosis of the adrenal gland, whereas much thought has been devoted to an understanding of pulmonary tuberculosis. This may be due in part to the relative rarity of adrenal involvement when compared to that of the lungs. An additional handicap was the unavailability of an experimental model in which to study adrenal infection, whereas some of the pulmonary lesions were readily reproduced. A few attempts at infecting the adrenals with tubercle bacilli were not successful in reproducing the disease picture seen in man.[4] None of the commonly employed laboratory animals used in studies of tuberculosis develop adrenal lesions. It is the purpose of this paper to apply to man the experience gained from experimental studies in animals.

EXPERIMENTAL MODELS

During a study of chronic toxoplasmosis in Golden hamsters, adrenal infection and necrosis were occasionally observed several months after the initial infection.[5] These lesions occurred too infrequently and too unpredictably to lend themselves to experimental study. More recently, however, adrenal involvement was encountered commonly in hamsters infected with another obligate intracellular protozoan, *Besnoitia jellisoni*.[6] Adrenal lesions were found in about one half of the animals that died after chronic infection of several months' duration. They were produced by organisms multiplying in adrenocortical cells, while other organs were involved with what appeared to be a reasonably well-equilibrated or latent

*The work described in this paper was supported in part by research grants E-826 and E-1644 from the National Institute of Allergy and Infectious Diseases, Public Health Service, Bethesda, Md.

chronic infection. By proper adjustment of the infectious inoculum and of chemoprophylaxis, adrenal necrosis visible in the gross could be caused to occur in about 80 per cent of these hamsters as early as two weeks after infection. This was a period of time when immunity emerged, as indicated by the regression of some of the visceral lesions.

It was shown in these subacute and also in chronic infections that the peculiar susceptibility of the adrenal cortex was abolished following surgical hypophysectomy as well as after the administration of cortisone, both of which produced adrenocortical atrophy, presumably due to lack of adrenocorticotrophic hormone (ACTH). The administration of ACTH to hypophysectomized hamsters restored a measure of susceptibility to infection of the adrenal glands. Also, during the course of subclinical chronic infection, the administration of glucocorticoids in pharmacological doses led to a recurrence of generalized proliferative activity by *Besnoitia,* without selective adrenal involvement, although frequently the tissues surrounding the subcutaneous injection sites of cortisone acetate were parasitized. Hence, although involvement of the adrenal gland appeared to depend on a supply of endogenous or exogenous ACTH, it appeared more reasonable to implicate steroids produced by the adrenal cortical cells, since injection of corticoids, but not of ACTH, predisposed to relapse of infection with parasitization of the subcutaneous injection sites.[6,7,8,62]

After the role of corticoids in the pathogenesis of adrenal infection had become clear in hamsters, I became impressed, while reviewing slides of the student collection on tuberculosis, by the marked difference in the appearance of tuberculous lesions in the adrenal and those elsewhere in the body. The typical epithelioid and giant cell reaction was almost absent in the adrenal gland; instead, extensive necrosis was more prominent than in any other organ of the same patient.

In a review of the role of hormones in experimental tuberculosis, Lurie[9] described a number of striking differences in the appearance of lesions of rabbits when treated with pharmacological doses of cortisone. These are pertinent to the understanding of the adrenal lesions in man. Lurie's observations are summarized in TABLE 1.

The adrenal lesions in man resembled those of cortisone-treated rabbits. Similar lesions were observed in generalized tuberculosis of human beings treated with cortisone, and in hamsters with mycobacterial infections.[10] Likewise in cortisone-treated hamsters with *Besnoitia* infection, lesions showed larger numbers of organisms and a limited inflammatory reaction when compared to eucorticoid controls. However, the discrepancy in lesions between untreated and cortisone-injected animals was more striking in mycobacterial infections, in view of the complex granulomatous reaction accompanying them.[10,63]

TABLE 1

	Untreated	*Pharmacological doses of cortisone*
(a) Number of lesions	1+	4+
(b) Size of tubercles	Larger	Smaller
(c) Type of pulmonary lesions	Discrete granulomata	Caseous pneumonia
(d) Caseation	Advanced	Partial
(e) Autolysis	Cellular boundaries and nuclei disappeared	Cell and nuclei recognizable
(f) Perifocal inflammation	Wide zone	Sharply delimited
(g) Capillary proliferation	2+	±
(h) Macrophages	Tend to digest bacilli	Support growth of bacilli
(i) Number of bacilli	Moderate	Large
(j) Epithelioid cell maturation	Normal	Decreased

COMPARISON OF ADRENAL AND EXTRA-ADRENAL LESIONS

Materials and Methods

Human autopsy material was reviewed. In all cases periodic acid-Schiff hematoxylin staining and Gridley's chromic acid-Schiff method were employed in a search for fungi, and Fite's fuchsin-formalin for acid-fast bacilli,[13] irrespective of the original diagnoses. Cases in which an etiological diagnosis could be made were tabulated as follows: (1) Addison's disease (TABLE 2); (2) disseminated infections with adrenal lesions (TABLE 3); and (3) lesions from patients treated with corticoids or ACTH (TABLE 4).

In addition, 55 cases coded as "Addison's disease," or as "necrosis of the adrenal glands," were reviewed from the files of the Armed Forces Institute of Pathology, Washington, D. C., to check on the validity of the conclusions drawn from the more limited number of cases readily available locally.

Lesions in the various organs were evaluated according to the following criteria: (1) selectivity of organ involvement and degree of destruction; (2) tissue reaction, with occurrence of (a) necrosis, (b) inflammatory cells, (c) epithelioid cells, (d) giant cells, and (e) fibrosis; (3) number of organisms present; and (4) factors from adrenal glands imparting susceptibility to adjacent organs.

TABLE 2

LESIONS IN PATIENTS WITH ADDISON'S DISEASE

Case No.	Age and sex	Duration terminal illness	Organ	Weight (comb.) grams	Degree involvement	Predominant tissue reaction: Necrosis	Neutrophils	Lymphocytes	Plasma cells	Macrophages	Immature epith.	Epithelioid	Giant cells	Fibrosis	No. organisms	Source
			Histoplasmosis													
1	49 WM	8 mo.	Adrenal	400	98%	+++									5	715[52]
			L. node various		Min.										1-2	
			L. node mesenteric		Marked	+				+		+			4-5	
			Peyer's patches		Marked	+				+				+	4-5, ulcer	
			Liver	1750	Min.			+						+	2, with Gridley stain	
			Liver adj. adrenal		Marked	++		+	+	+	+	+	+	+	5, discussed with case 24.	
			Prostate		Mod.					+				+	5	
			Brain	1375	Min.	++			+	+	+				5, perithelial cell granuloma	
2	42 WM	2 mo.	Adrenal			+++		+							5	XVIII-9
			Liver												0?	
3	61 WM	7 mo.	Adrenal	120	100% (?)	+++		+							5, without nuclei	XXX-80
			Liver		Mod.							+	+	+	0	
			Spleen		Mod.	+						+	++		0	
			Lung		Marked	+						+	+	+	0, AFB neg	
4	65 WM	6 mo.	Adrenal	55	90%	+++		+							5, also hyphae	42-79 AFIP 838756
			Liver		None (?)	fungal hyphae only										
			Spleen		None (?)	fungal hyphae only										
			Kidney		None (?)	fungal hyphae only										
	Histoplasmosis previously diagnosed as sarcoidosis															
5	56 WM	7 mo.	Adrenal	302	99%	+++		(+)	(+)				(+)	(+)	5, without nuclei { Fibrosis from medulla, also giant cells	AFIP 121747[11]
			Liver	3100	Min.			++				+	+		0	
			Lung	2200	Mod.	+				+++		++	++		0	
			Spleen	1300	Mod.							++	+		0 reticular cell hyperplasia	
			L. node		Min.-Mod.							+	+		0 reticular cell hyperplasia	

6	26 WM	8 mo. to 3 yr.	Adrenal Liver Lung Spleen L. node Kidney Bone Marrow	80 1200 	90% Mod. Min. Max. Min.-Marked Mod. Marked	+++ + + 	+ + + 			+		++ ++ +++ +++ ++ ++	++ ++ ++ ++ ++ ++	 + +	5, with nuclei 4, mostly without nuclei 2 4, mostly without nuclei 2-5 4 4	AFIP 121022[11]
7	30 WM	8 mo.	Adrenal Liver Lung Spleen L. node	95 575 	99% Min. Mod. Marked Marked	+++ 	+			+ ++ 		(+) + + ++ ++	(+) + + ++ ++	 + +	5, with and without nuclei 0 2, without nuclei 0 0 Amyloid	AFIP 119987[11]
8	50 WM	13 mo.	Adrenal } p Rx with Liver } ampho- Spleen } tericin B L. node, before Rx	45 ± 400 	100% Mod. Marked Max.	+++ + 	 + +	 	 	+ + 	 + 	 + + +	 + +	+ + + +	5, without nuclei 0 0 2	CAH Hertzler Cl. No. 40818*
			Tuberculosis												
9	65 WM	Sudden death	Adrenal Lung	20 	80% Min.	++ 	 	+	 	 	+	 + 	+ + 	 + +	2, active areas, next to cortex 0, no viable cortex in lobe 0	185
10	44 CF	Sudden death with asthma	Adrenal Liver Spleen	15 	95% Min. Min.	+++ + +	 	+ + + +	+ + 	 	 + + +	 + +	+ + 	 + 	2, next to cortex Figure 19 0, older areas 0 0	292[53]
11	60 WM	2 d.	Adrenal Lung	±	95% Mod.	+++ +	 	+ +	 	 	+ 	 ++	 +	 +	2 0	KC. V. A. 53-P-65
12	64 WF	7 d.	Adrenal Lung	+	100% Min.	+++ +	 	+ +	+	 	 	 +	 +	 	0, Gridley stain negative 0, Clinical diagnosis	XXXVI-217

LEGEND:

Degree of Involvement

Per cent estimated for adrenals on

90-100% maximal
~ 50% marked
~ 10% moderate
< 5% minimal

Number of Organisms

0 None seen
1 None seen, cultured
2 Few, less than 1 per lesion
3 Frequent, one per lesion
4 Numerous, several per lesion
5 Very numerous, often several per cell

Tissue Reaction

+++ Ranked for each organ
++
+
( ) Reaction in the absence of viable adrenal cells, in adrenal capsule or medulla.

Blank indicates that finding was not observed.

*C. A. Hellwig, C. Pokorny, and R. Montgomery-Short, personal communication.

TABLE 3

ADRENAL AND EXTRA-ADRENAL LESIONS IN PATIENTS WITH DISSEMINATED INFECTIONS

Case No.	Age and sex	Duration terminal illness	Organ	Weight (comb.) grams	Degree involvement	Predominant tissue reaction: Necrosis	Neutrophils	Lymphocytes	Plasma cells	Macropheges	Immat. epith.	Epithelioid	Giant cells	Fibrosis	No. organisms (inclusions)	Source
			Tuberculosis													
13	57 WM	1 yr.	Adrenal	35	75%	+++		+	+	+					2	54-P-37
			Liver	2300	Min.	+		+				+	+	+	0	Kansas City V.A.
			Lung	510	Mod.	+		+		+		+	+	+	2	Hospital
			Kidneys		Mod.	+		+		+		+	+	+	2	
			Prostate		Marked	+		+	+	+		+	+	+	0	
14	56 WF	9 d.	Adrenal	10	80%	+++		+							5	XXXV-109
			Liver	1000	Min.	+		+				+			4	
			Lung	700	Marked	+								+	4	
			L.node		Marked	+								+	5	
15	85 WM	several years; hospital, 1 week	Adrenal	10	30%	++		+							5	49-191
			Liver	1200	Mod.	+						+	+	+	2	
			Lung	1980	Mod.	+	+					+			3	
			Spleen	450	Mod.	+						+	+	+	3	
16	65 WF	9 d.	Adrenal	10	20%	++		+							3	45-95
			Liver	1190	Min.	+				+		+	+	+	0	(St. Joseph's
			Lung	1290	Marked	++		+		+		+		+	4	42-45)
			Spleen	165	Mod.	+						+	+		0	
17	52 CM	? hospitalized 1 day	Adrenal		20%	++		+	+						5	43-2
			Liver		Mod.	+		+				+	+	+	3	
			Lung		Mod.	+		+				+			4	
			Spleen		Mod.	+									3	
			Pericardium		Marked	+		+	++	+		+	+	+	0	
			Kidney		Min.	+		+	+						0	
			L.node		Max.	+++				+		+	+	+	4	
			Coccidioidomycosis													
18	5 WM	1-4 yr.	Adrenal	20 est.	80%	++	+	+		+	+		+		4	XXI-197
			Lung		Mod.							+	+	+	4	
			Meninges		Marked			+	+			+	+	+	4	

			Varicella													
19	13 d. WF	5 d.	Adrenal		10%	++									4 (Intranuclear inclusions)	A-167-57 Toronto H.S.C.[54]
			Liver		Mod.	++		+							0	
			Lung		Mod.	++				+					4	
			Spleen		Min.	+									0	
			Skin		Marked	++	+								5	
			Herpes Simplex													
20	8 d. M	4 d.	Adrenal		30% of outer cortex		Inclusions in every nucleus									Toronto H.S.C.
			Liver		80%		Inclusions in 1/2 of nuclei									
21	9 mo. M	11 d.	Adrenal		20%	+++	(+)	(+)							4	138-54 Gt. Ormond St. Hosp. London[14]
			Skin		20%	++	+								4	
			Cytomegalic Virus													
22	63 M	(8 months myelog. leukemia)	Adrenal	18	10%	++	Inclusions in fasciculata									A57-163[36]
			Liver	1600	1%	+	Inclusions in liver bile duct cells									
			Spleen	375	5%	++	Inclusions in reticular cells of follicle, sinusoids									
			Lung	1550	10%		Inclusions in alveolar lining cells									
			Histoplasmosis													
23	6 WM	24 d.	Adrenal	9	Min.										3	439
			Lung	540	Marked					+					5	
			L. node mediastinal		Max.	+++									5	
			L. node mesenteric		Min.										3	
			Liver	1100	Marked	+++		+							5	
			Spleen	380	Max.	++ +									5	

LEGEND:

Degree of Involvement

Per cent estimated for adrenals only
90-100% maximal
~ 50% marked
~ 10% moderate
< 5% minimal

Number of Organisms

0 None seen
1 None seen, cultured
2 Few, less than 1 per lesion
3 Frequent, one per lesion
4 Numerous, several per lesion
5 Very numerous, often several per cell

Tissue Reaction

+++ Ranked for each organ
++
+
( ) Reaction in the absence of viable adrenal cells, in adrenal capsule or medulla.
Blank indicates that finding was not observed.

TABLE 4

COMPARISON OF LESIONS IN PATIENTS TREATED WITH CORTICOIDS OR ACTH

Case No.	Age and sex	Duration terminal illness	Rx	Daily dose mg.	Duration (days)	Adrenal Lesions: Weight grams	Involvement	Tissue reaction	No. organisms	Extra-Adrenal Lesions: Organ	Degree involvement	Tissue reaction	No. organisms	Source
		Histoplasmosis												
24	49 WM	8 mo.	Cortisone p.o.	25 50 37	7 30 30	400	98%	IG leading to N	5	Lymph node periaortic axillary mediastinal	Min.	None	1-2	715[52]
	(same as case 1)									Lymph node mesenteric	Marked	M,E,N	4-5	
										Peyer's p.	Marked	M,F,N, ulcer	4-5	
25	43 WM	1-4 yr.	Cortisone p.o.	75	30	80-100	95%	In N area	5	Only rare and isolated Histoplasma seen			1-2	1156
			Cortisone p.o.	150	60									
			Cortisone i.m.	150	30			Surviving and regenerating cortex	2	(Cortisone injection sites and regional lymph nodes not examined)				
			Corticosterone p.o.	300-450	14									
26	65 WF	9 mo.	Cortisone p.o.	25	30	20	20%	IG in cortical and sinusoidal lining cells, rare N	5	Liver	Marked	IG, N	5	55-62
			Cortisone p.o.	50	135					Bone marrow	Max.	IG, N	5	Trinity Lutheran
										L.node peribr.	Complete	N		
			Prednisone p.o.	30	45					L.node mesent.	Lymphoid atrophy		5	
										reticular cell hyperpl.		N		
			Prednisone p.o.	10	45					Lung	Min.	IG,M	2-3	
			Prednisone	20	8									

	Cryptococcosis													
27	65 WM	4 mo.	Hydrocortisone, i.m. None	100 50	7 19 5	16	10%	Right-focal necrotizing reactions, some of which are surrounded by rim of fibroblasts and GC. Lipid largely preserved. Left-central vein thrombosis s Crypto	5	Meninges-crypto. in GC and in N exudate, F,P,M,L. Choroid plexus, MA with surrounding fibroblastic proliferation GC, L			4	2083 (AFIP 846199)[6 1]
28	71 WF	5 wk.	Cortisone i.m.	100	3		2%	Focal N,L,M	4	Meninges Kidney	Marked Min.	M,MA,N Focal M,GC,F	5 5	57-72 Trinity Lutheran
29	48 WM	4-7 mo.	ACTH gel ACTH gel ACTH gel	40-80 units 20 u 40 u	7 28 10	"normal"	5%	Focal N,IG, with occ. PMN,L	5	Liver Lung Kidney	Min. Mod. Mod.	PMN, L,M,GC M PMN, M, F	4-5	BA-11-53 Good Samaritan LA
	Tuberculosis													
30	62 WM	5 wk.	Prednisone p.o. None Cortisone	20 200	19 2 4	23		No lesions Lipid preservation: Mod. Birefringence: Mod.	0	Liver LN Spleen Lung Ghon lesion (Aspiration pneumonia with Pseudomonas, Proteus, Aerobacter, Aspergillus-like fungus).	Mod. Marked Min. Min.	N, L, IE, GC N (inc) IE, GC IE, N, GC IE N, F	3 4 2 2 4	1708

LEGEND:

E, epithelioid cells; F, fibrosis; GC, giant cells; IE, immature epithelioid cells; IG, intracellular growth; L, lymphocytes; M, macrophages; MA, microabscesses; N, necrosis; P, plasma cells; PMN, polymorphonuclear neutrophils; p.o., by mouth; i.m., intramuscularly.

Results

Cases of Addison's disease. The contrast in the reactions which *Histoplasma* and tubercle bacilli evoke in the adrenals as compared to other organs is well illustrated (TABLE 2). In all cases necrosis is more extensive in the adrenals, to which it is frequently confined (FIGURES 1 to 6). This is particularly marked in cases 5 to 8, originally diagnosed as sarcoidosis on account of the well-developed epithelioid reaction without significant necrosis. In the adrenals, however, necrosis and destruction were nearly complete, while epithelioid and giant cell reaction and fibrosis were minimal. When present, they were found in areas where all adrenocortical cells had been destroyed (FIGURE 19).

Of interest is the apparent greater degree of enlargement of adrenals involved with histoplasmosis (FIGURE 2). The impression was gained that compensatory hyperplasia accounted for most of the adrenal enlargement in histoplasmosis, while there is little evidence that this process was effective in tuberculous adrenals.

Data regarding the numbers of organisms are summarized in TABLE 2. It will be observed that in all cases organisms are most numerous in the adrenals. *Histoplasma* in viable adrenal cells generally contained nuclei staining with hematoxylin. Such nuclei were absent in the necrotic areas, suggesting that host cell necrosis might also be fatal to *Histoplasma.* Anucleate ring forms of *Histoplasma,* as demonstrated by Gridley's method,[13] were exclusively present in the necrotic adrenals of cases 3 and 5, and also in those of patient 8 who, after treatment with amphotericin-B and apparent cure, died several months later in an Addisonian crisis. In other organs, anucleate *Histoplasma,* sometimes in large numbers, were accompanied by granulomatous reaction, as indicated in TABLE 2.

Disseminated infection with adrenal lesions. In tuberculosis and coccidioidomycosis, the dimorphism between adrenal and extra-adrenal lesions is again demonstrated (TABLE 3). In tuberculous adrenals, a necrotizing reaction is predominant, accompanied by slight lymphocytic infiltration. In the other organs, epithelioid and giant cell reaction and fibrosis generally prevail (FIGURES 5 to 6). Granulomatous reaction was found in the adrenals of the patient with coccidioidomycosis, where giant cells were present together with small, immature epithelioid cells; however, they were large and mature in the lung and meninges, where necrosis was absent (FIGURES 8 to 10).

The numbers of microorganisms in the adrenals were generally larger than in the other organs involved. An exception presented the child with acute fulminant histoplasmosis, who exhibited but slight adrenal involvement without discrete foci of necrosis (case 23).

In cases 19 and 20, representing varicella and herpes of newborn infants, there was so little inflammatory reaction as to make comparison impossible. In case 20, the focal herpetic lesions in the adrenals showed intranuclear inclusions in each cell, while the liver was more severely and diffusely involved as an organ, with fewer inclusions per unit area. In case 21, the nine-months-old child with herpes, the adrenals were the only organs involved apart from the skin. In contrast to the two newborns (cases 19 and 20), the provisional adrenal cortex was no longer present here. The necrosis was focal but extensive, with inflammatory cells present at the borders of the lesions only in the medulla, but not in the adrenal cortex. Apart from this subtle difference in inflammatory reaction within the adrenals, it was felt that no comparison could be drawn to the skin lesions, since slight secondary infection was probably present there. However, the contributors of this case, by means of chick embryo and mouse inoculations, found more virus in the adrenals than in the skin and other organs of this patient.[14] Case 22, with cytomegalic infection, showed greater involvement and necrosis of adrenals than of liver (FIGURES 17 and 18). Inflammatory reaction was minimal.

Analysis of Lesions in Patients Treated with Corticoids or ACTH

Since endogenous corticoids permit increased microbial proliferation, modify the granulomatous reaction, and enhance necrosis in the adrenals, it could be expected that patients treated with pharmacological doses of such corticoids might show *generalized* lesions resembling those described in adrenals (TABLE 4). In addition, progression of adrenal parasitization might be modified consequent to the corticoid-induced pituitary-adrenal hypofunction. To analyze better the complex effects of corticoids and ACTH on adrenal and extra-adrenal sites, a number of cases will be examined in detail.

Case 24

The effect of relatively small doses of corticoids, given orally, on the lesions in the intestine and mesenteric lymph nodes is illustrated by this case. It also indicates that endogenous corticoids draining via the liver from an adherent adrenal impart greater susceptibility to involvement with *Histoplasma* to the lobe of liver which is adherent (case 1, TABLE 2).

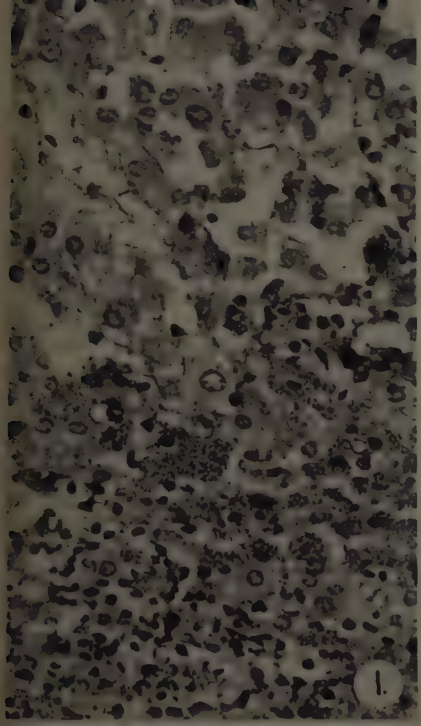
The patient was a 45-year-old male oil driller who, 8 months before death, became short of breath, developed afternoon fever, weakness, malaise, night sweats, and cough. He became emaciated and showed lesions in the right apex radiographically. Three months before death, positive physical findings included a blood pressure of 90/70, generalized hyperpigmentation, hepatomegaly, and palpable lymph nodes. His

FIGURE 1. Histoplasmosis. Case 1. Transition from intact adrenal cortex to necrotic area. Numerous Histoplasma are present in cortical and sinusoidal lining cells in this zone; their nuclei stain less densely in necrotic area. This is from an area of subcapsular compensatory hyperplasia. Hypertrophy of intact cortical cells is indicated by the amount of cytoplasm. Periodic-acid Schiff, hematoxylin (PASH). × 262.

FIGURE 2. Histoplasmosis. Case 1. Posterior view of cross section through right adrenal and kidney. This adrenal and the contralateral one were completely necrotic and markedly enlarged. The adrenal is adherent to both kidney and liver.

FIGURE 3. Histoplasmosis. Case 1. Transition from liver, with marked chronic inflammation *(above)* to complete necrotic adrenal *(below)*. The thickened liver and adrenal capsules are in the center. Numerous ghost forms of *Histoplasma* are found in the necrotic adrenal and, to a lesser extent, in the capsule. While few viable organisms are also present in the liver and its capsule, they are not so numerous as in liver tissue adjacent to still viable cortex. Periodic-acid Schiff, hematoxylin. × 79.

FIGURE 4. Histoplasmosis. Case 25. Transition from viable, but hypofunctional cortex *(above)*, which is free of organisms, to necrotic cortex *(below)*, where numerous anucleate *Histoplasma* are present. Period of corticoid-induced adrenal hypofunction 3½ months. Hematoxylin and eosin *(left)*, Gridley's fungus stain *(right)*. × 159.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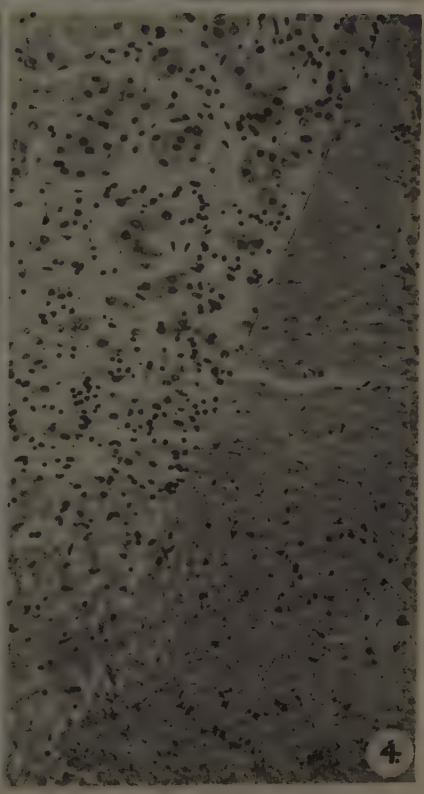
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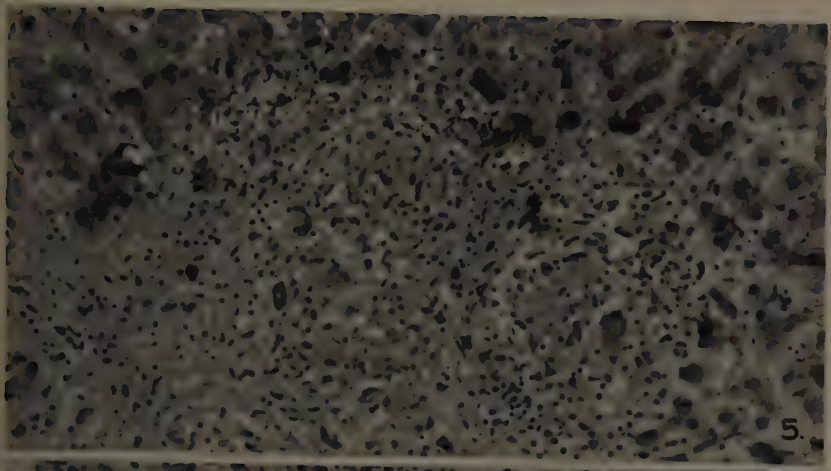
FIGURE 5. Tuberculosis. Case 13. Well-developed granuloma showing lymphocytes, epithelioid cells, giant cells, and fibrosis, but little necrosis. Hematoxylin and eosin. × 152.

FIGURE 6. Tuberculosis. Case 13. Adrenal. There is almost complete absence of a granulomatous reaction in this slide as compared to FIGURE 5. The lesion is essentially an area of caseation necrosis, surrounded by scanty lymphocytes, plasma cells and macrophages. Slide 74 of student slide collection that stimulated this study. Hematoxylin and eosin. × 152.

FIGURE 7. Tuberculosis. Case 30. Predominantly necrotic reaction in liver of patient treated with corticoids for 3 weeks prior to death. The lesion resembles that in the adrenal (FIGURE 6). Note absence of typical granulomatous reaction as shown in FIGURE 5. The process of caseation is incomplete. Fibroblastic and mononuclear reaction is slight in tubercles from liver and other organs of this patient. Hematoxylin and eosin. × 152.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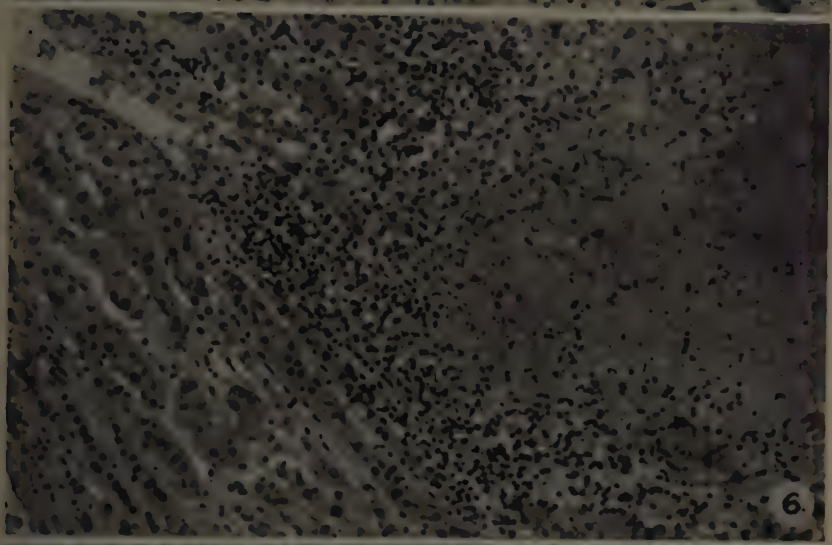
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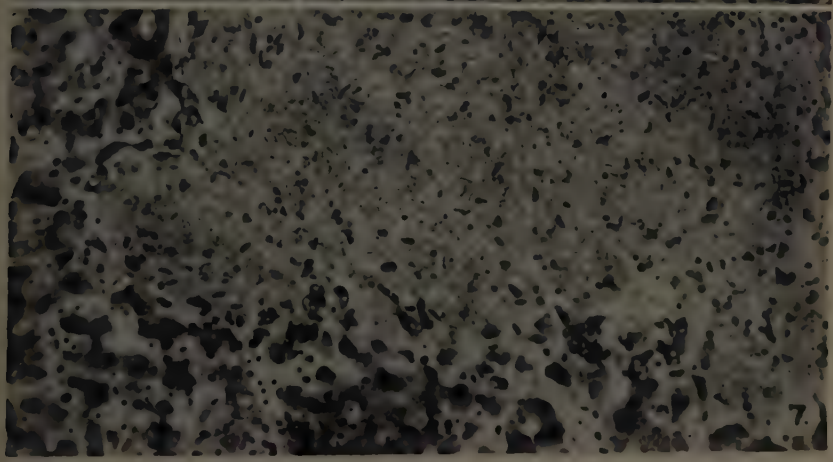
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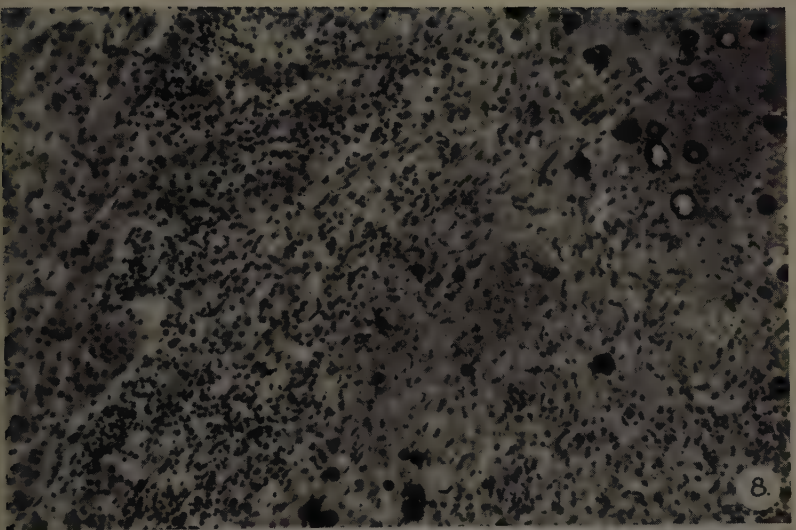
FIGURE 8. Coccidioidomycosis. Case 18. Adrenal. An abortive granuloma tous reaction is present here, as compared to the well-developed granuloma i the lungs and meninges (FIGURES 9 and 10). Epithelioid cells are thin an spindly, and a few giant cells are present. Numerous lymphocytes and macro phages are seen close to the cortex. The dark-staining fungal spherules ar generally accompanied by necrosis. Periodic-acid Schiff, hematoxylin. × 152.

FIGURE 9. Coccidioidomycosis. Case 18. Lung. Organisms are found onl in scattered fibrosing granulomas. Period-acid Schiff, hematoxylin. × 152.

FIGURE 10. Coccidioidomycosis. Case 18. Meninges. Fungi are accompanie by fresh and fibrosing granulomatous reaction. They are frequently contained i multinucleated giant cells, as in the left half of picture. Period-acid Schif hematoxylin. × 152.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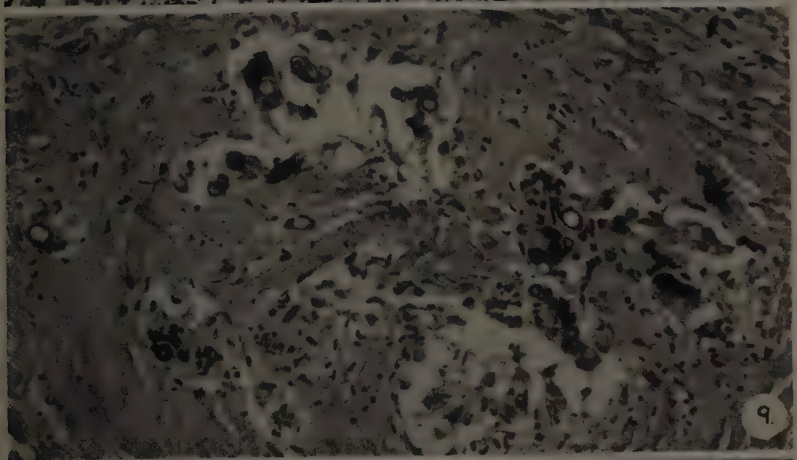
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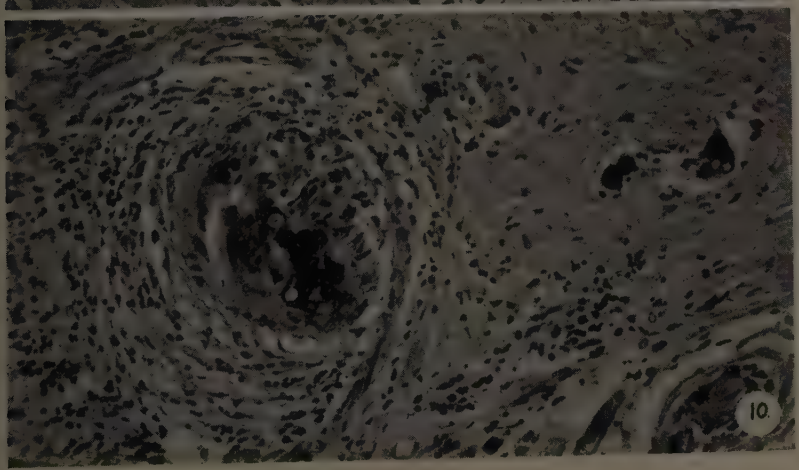
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FIGURE 11. Cryptococcosis. Case 29. Adrenal. Numerous small fungi are found intracellularly in sinusoidal and cortical cells. Cellular reaction is almost absent. Cortical cells are hypertrophic with pale, finely granular cytoplasm in this patient treated with corticotrophin for 6 weeks. Periodic-acid Schiff, hematoxylin. × 260.

FIGURE 12. Cryptococcosis. Case 28. Adrenal. One of few foci of necrosis containing many irregularly sized fungi *(arrows)* intra- and extracellularly, accompanied by lymphocytes and macrophages. Adrenal capsule near top (see FIGURE 15 for meningeal lesions). Periodic-acid Schiff, hematoxylin. × 60.

FIGURE 13. Cryptococcosis. Case 27. Adrenal. Intact cortex *(above)* is separated from large main area of necrosis by an outer zone of pale fibroblasts and epithelioid cells and an inner zone of multinucleate giant cells. Fungi (pale) are numerous in the necrotic debris and in the giant cells. This is the only case where a well-defined granulomatous zone was found in the adrenals. This patient had been under the influence of corticoids for 4 weeks. The pharmacologically induced adrenal hypofunction is believed to have permitted the fibrosis and giant cell reaction to develop (see FIGURE 16 for meningeal reaction). Periodic-acid Schiff, hematoxylin. × 151.

FIGURE 14. Same gland as shown in FIGURE 13. This shows an extension from the main focus of cryptococcal proliferation *(arrows)* with necrobiotic cells (below). There is no transitional zone toward the cortex (*above*). This lesion is younger than the chief one shown in FIGURE 13 and probably arose when corticoidogenesis recurred during the last five days of the patient's life. Periodic-acid Schiff, hematoxylin. × 260.


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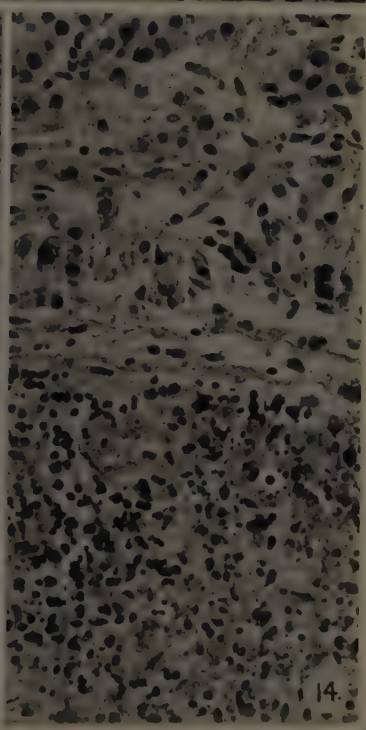
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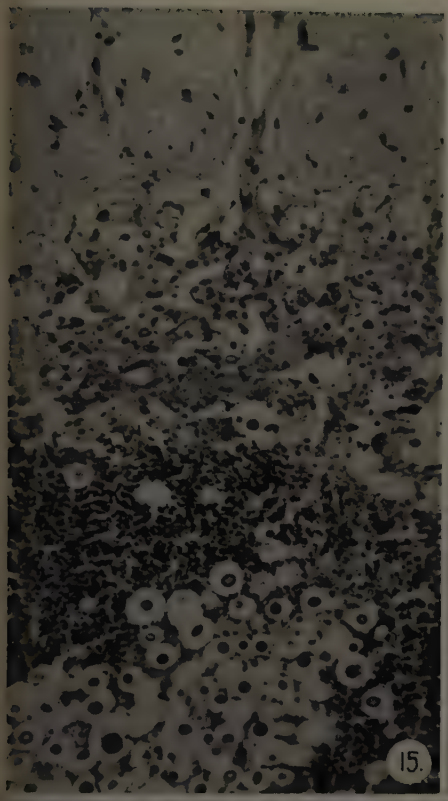
FIGURE 15. Cryptococcal meningitis. Case 28. Fungi are numerous in the lower field. The acute necrosis of most of the mononuclear cells in the exudate is unusual for cryptococcal meningitis. This patient had been treated with 100 mg. of cortisone daily for the last three days of her life (see FIGURE 12 for adrenal lesion). Periodic-acid Schiff, hematoxylin. × 144.

FIGURE 16. Cryptococcal meningitis. Case 27. In this case, as in FIGURE 15, there is much necrotic exudate, some of which is shown in the right lower corner. This is surrounded by a zone of multinucleate giant cells in the lower half of the field, with fibroblastic and vascular proliferation. Lymphocytes are seen peripherally, next to the cerebral cortex above. Cryptococci *(arrows)* are numerous in the necrotic exudate and in the giant cells (compare with FIGURES 13 and 14 for adrenal lesions). Periodic-acid Schiff, hematoxylin. × 144.

FIGURE 17. Cytomegalic virus infection. Case 22. Adrenal. Enlarging focus of necrosis resulting from infected cells with intranuclear and intracytoplasmic inclusions such as are seen in the periphery (compare with FIGURE 18). Hematoxylin and eosin. × 144.

FIGURE 18. Cytomegalic virus infection. Case 22. Liver. Two cells with inclusions. Involved cells were rare and always single (compare with adrenal lesions, FIGURE 17). Hematoxylin and eosin. × 238.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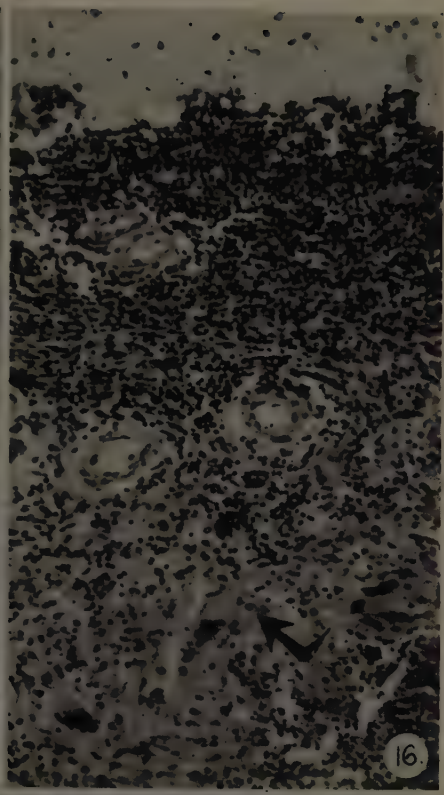
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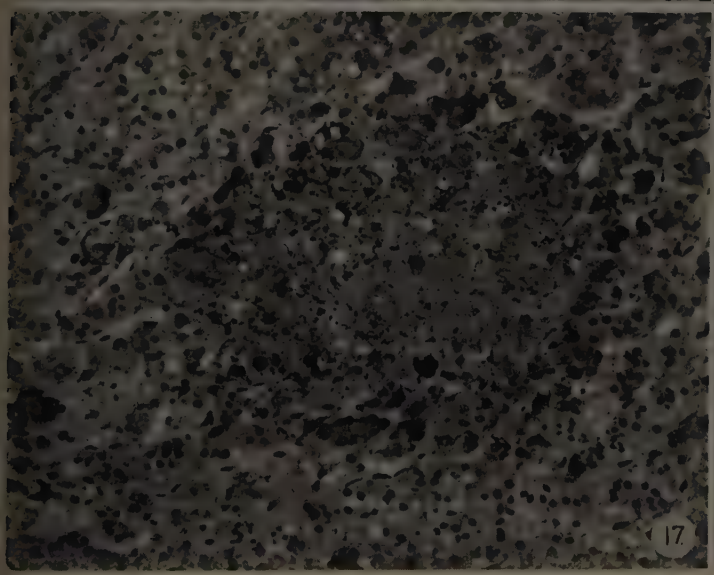
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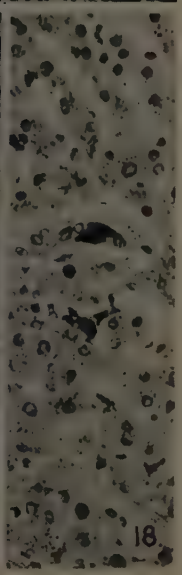
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FIGURE 19. Tuberculosis. Case 10. There is an abrupt transition from viable adrenal cortex (C) to necrosis (N). Granulomatous reaction (G) develops from the capsule on the left and lower border of the necrotic area, but fades out (*arrow*) as it approaches the cortical nodules. Hematoxylin and eosin. ×35.

histoplasmin skin test was positive. Biopsy of a cervical lymph node showed *Histoplasma*, which was also obtained by culture from blood and bone marrow 2 months prior to death. He was treated with cortisone, 25 to 50 mg. orally per day and with desoxycorticosterone acetate, varying from 2 to 15 mg. daily. He received a course of hydroxystilbamidine followed by β-diethyl aminoethyl fencolate*without apparent improvement. The patient's electrolyte balance appeared to be most difficult to maintain, and he died in an Addisonian crisis.

The adrenals were grossly enlarged, with a combined weight exceeding 400 gm., and they were replaced by two moderately firm caseous masses (FIGURE 2). Microscopically, necrosis was almost complete and consisted of microbial as well as infarction necrosis. Small islets of surviving and regenerating adrenal cortical cells were found adjacent to and in the adrenal capsule. Most cortical and sinusoidal lining cells contained *Histoplasma*. At the periphery of these cortical remnants, cytoplasmic basophilia increased, and the cells became necrotic without the accompaniment of inflammatory cells or epithelioid reaction (FIGURE 1).

The liver presented a normal picture, grossly and microscopically, except in the immediate vicinity of the areas where the adrenals had become attached (FIGURE 3). Here, where the liver apparently drained blood from the surviving adrenal cortical nodules, disorganization of lobular pattern and fibrosis were evident in the gross. There was much fibroblastic proliferation accompanied by mononuclears with foci of epithelioid cells, giant cells, and occasionally necrosis. Although small numbers of *Histoplasma* were present in the cells constituting the granuloma, they were rarely found in liver or Kupffer's cells.

Adjacent to the kidneys, no remaining adrenal cortical islands were found. The fused adrenal and renal capsules were involved by granulomatous inflammation with small numbers of *Histoplasma* present. The kidneys showed a picture consistent with lower nephron nephrosis.

The lungs contained a number of fibrocaseous areas in which rare tubercle bacilli were found on sections. Small numbers of *Histoplasma* were seen in the right apex only.

Spleen, mediastinal, and periaortic lymph nodes showed moderate lymphoid depletion and some reticular cell hyperplasia. No fungi or tubercle bacilli were identified, although three months previously biopsy of a cervical lymph node presented complete transformation into sheets of epithelioid cells containing numerous *Histoplasma* and some areas of necrosis. However, several ileal ulcers which overlay Peyer's patches showed fields of macrophages which extended into the muscularis interna. Almost all of the macrophages contained several *Histoplasma* organisms. The mesenteric lymph nodes exhibited a moderate degree of reticular cell

*Drug 112, Wm. S. Merrill Company, Cincinnati, Ohio.

hyperplasia, with many organisms, although fewer than seen in the lymph node biopsy obtained three months previously.

In the brain, several lesions took the form of focal necrosis, surrounded by a narrow rim of inflammatory cells. Most of these were derived from the perivascular tissue and laid down reticulum, while a few were plasma cells, astrocytes, and microglia. Many of the reticular cells contained *Histoplasma*.

Prostatic lesions consisted of diffusely distributed foci among apparently normal tissue, where almost every stromal cell contained fungi and where the glands were filled with fungus-laden macrophages, while the epithelial lining was apparently not parasitized.

Summary and interpretation. While this patient had widely disseminated histoplasmosis three months previously, active proliferation of *Histoplasma* had been restricted at the time of his death, indicating an increase in over-all immune status. It is doubtful that chemotherapy accounted for this.[12] In contrast to other organs, involvement was most advanced in the adrenal glands, where almost every remaining cell was parasitized and, essentially, the entire organ was destroyed. It was apparent that the adrenals showed the greatest immunological deficit, interpreted as being due to the corticoids elaborated by the adrenal cells. Areas of the liver that drained the vascular bed of the remaining and the regenerating cortical islands showed moderate to marked parasitization, with mixed granulomatous reaction and fibrosis, indicating a process of long standing. Liver away from the adrenals did not support the growth of *Histoplasma*.

The parasitization of Peyer's patches of the ileum and of the regional mesenteric lymph nodes, in the absence of lesions at the time of autopsy in the other lymph nodes, suggests the possibility that the orally administered cortisone depressed the immune potential in those areas where it was absorbed. Hence, only these lesions are listed in TABLE 4 as under the recent influence of exogenous corticoids. In view of the marginal doses of cortisone given, considering the patient's probable need, it is believed that they exerted but slight if any ACTH-blocking effect, insufficient to stop corticoid synthesis and parasitization of the adrenal remnants. Regenerating cortex was less markedly parasitized, suggesting either that some ACTH blockage was present, or that these cells were less responsive, or that they secreted corticoids of low immunity-depressing potential, such as aldosterone.

It appears difficult to explain involvement of the prostate gland, although the selective parasitization of the stroma, leaving the epithelium uninvolved, would point to some specific factors as being operative here. The focal lesions in the brain are believed to result from septic emboli into an area where the immune potential is naturally low.

Case 25

This case illustrates that, in a patient treated with large doses of corticoids, adrenal cells may show only few *Histoplasma*. The patient was treated with corticoids in doses that probably inhibited ACTH release for 4½ months prior to his death.

This patient's illness appeared to have started about 4 years prior to his death when he developed an ulcer on the left side of the tongue that healed after 3 months. An ulcer recurred there 18 months prior to death and never healed. The patient lost 30 pounds of weight and entered the hospital with a blood pressure of 105/75, apparently emaciated and in acute pain. Biopsy of the tongue lesion showed *Histoplasma*, confirmed by culture and mouse inoculation. Subsequently, 2 of 5 sputum cultures and 1 of 5 blood cultures were positive; however, one liver biopsy was negative. The patient's hospital course was marked by hypoglycemic episodes, frequently accompanied by convulsions. He presented a serious feeding problem in view of his painful tongue lesion. Whenever he was fed by nasal tube for a few days, he developed pharyngitis and it was necessary to remove the tube. His blood pressure progressively decreased, and on his last admission it was 75/70. He was treated with β-diethyl aminoethyl fencolate and aminostilbamidine without apparent benefit. He also received cortisone acetate, 100 to 150 mg. daily, at first by mouth and later intramuscularly, and desoxycorticosterone acetate, 2 to 15 mg. a day, intramuscularly. He sustained a severe hemorrhage from his tongue lesion, which necessitated first cauterization and later hemiglossectomy. His medication was changed from cortisone acetate to corticosterone, 300 mg. daily, 2 weeks prior to death. The aim was to reduce adrenal steroidogenesis and to maintain him on a glucocorticoid of lesser anti-inflammatory and presumably lesser immunity-depressing potency.[6,8,62] Three days prior to death, the corticosterone dosage was increased to 450 mg. (it was given orally, since only tablets of the drug were available to us at that time). Cultures of sputum yielded hemolytic streptococci, hemolytic *Staphylococcus aureus* as well as *Pseudomonas*. The patient died following aspiration during a hypoglycemic episode.

Both adrenals were enlarged to about 7 × 5 × 3 cm. and weighed an estimated 80 gm. each. They were almost completely necrotic. There was ulcerative laryngotracheitis with bronchitis, bronchopneumonia, and abscess formation. *Histoplasma* were cultured from the spleen and adrenals and heavy growth of *Aerobacter aerogenes* was present in every culture taken.

Cross sections through the entire adrenal gland were cut, revealing only few areas of intact cortical cells. The necrosis was coagulative in nature and resulted in part from direct microbial destruction and, in part, as a consequence of infarction. Fungi were numerous in the necrotic

cortex. They appeared nonviable, as indicated by their pale-staining capsules, and by the absence of a nucleus that stained with hematoxylin. In the surviving cortex, *Histoplasma* were quite scarce (FIGURE 4). Elsewhere only an occasional organism was found. Large numbers of pale-staining organisms were present in a necrotic portion of a hilar lymph node, which was fibrotic and partially calcified.

Interpretation. It is postulated that this patient developed pituitary-adrenal hypofunction in consequence of the large doses of corticoids administered. This led to inability of *Histoplasma* to proliferate in the remaining adrenal cortical cells, which had reverted to the same immune status as the other cells of the body, which were essentially free of infection. The remaining cortical cells were large, but with little stainable cytoplasmic material, unlike the eosinophilic cytoplasm of cells under intense ACTH stimulation. It will be recalled that the corticoid dosages that this patient received were much larger than those given to case 24, where *Histoplasma* were found to remain in the adrenal cortical cells (FIGURE 1). It would appear that the present patient's immunity level was higher, since it was not impaired by the administration of 150 mg. of cortisone by mouth or intramuscularly. No foci of inflammation or of proliferation by *Histoplasma* were found. Possibly, aspiration pneumonia was aggravated by the cortisone administered, although corticosterone should have decreased this effect. An incidental finding was a pulmonary nodule containing fungi resembling *Cryptococcus*.

Case 26

An instance of subacute disseminated histoplasmosis in a patient who was treated with corticoids for essentially the entire period of her illness is shown by this case. The illness began with productive cough, malaise, diarrhea, and fever. Lupus erythematosus was suspected for want of anything suggesting a specific diagnosis. A renal biopsy, L.E. preparations, and bone marrow studies were not revealing. There was hypoalbuminemia and hyperglobulinemia with a total protein of 6 gm. The patient had had a splenectomy 12 years previously for what had appeared to be splenic neutropenia. Examination proved this spleen to be free of *Histoplasma*.

Contrary to findings in other adults with histoplasmosis (TABLES 2 and 4), this patient's adrenals were not significantly enlarged and they showed only 20 per cent involvement. The cortex was thin; the cells did not appear under the influence of ACTH. Although very numerous *Histoplasma* were present, mostly in sinusoidal lining cells, there was little necrosis. Liver, bone marrow, and lymph nodes, which likewise showed heavy parasitization, exhibited a greater tendency to necrosis.

Interpretation. Judging from the appearance of the adrenal cortex and consistent with the history of prolonged and significant corticoid admin-

istration, accompanied by two attacks of bacterial meningitis and a compression fracture of the left hip, there was nearly complete adrenal hypofunction. Assuming that levels of exogenous corticoids were of a comparable order of magnitude in different organs, one would conclude that liver, bone marrow, and lymph nodes supported better growth of *Histoplasma* than essentially nonsecretory adrenals under the conditions of corticoid-modified immunity prevailing. The pattern of organ involvement was similar to that found in acute fulminant histoplasmosis of children (case 23), where acquired immunity is insignificant and where biochemical substrates appear to determine the degree of parasitization in those tissues reached by fungi. It is believed that the marked dissemination occurred while the patient received 30 mg. of prednisone. Repeated blood cultures and a bone marrow smear taken prior to that time were devoid of organisms. The patient had also been taking 125 to 400 mg. daily of tetracycline or chlortetracycline for the last 5 months of her life. No intestinal ulceration (as in case 24) was found, and Peyer's patches were not available for microscopic sampling.

Case 27

This case is notable for two adjacent foci of adrenal necrosis containing cryptococci (FIGURES 13 and 14), one of which was surrounded by epithelioid-giant cell reaction, and for cryptococcal meningitis with microabscesses and giant cell reaction (FIGURE 16).

The patient's illness started with headache, vomiting, fever, and a stiff neck. *Klebsiella pneumoniae* was reported to have been cultured on two occasions from the spinal fluid. Three subsequent cultures, India ink preparations, and five blood cultures were recorded as negative. The patient remained stuporous during his entire hospital stay. Pharmacological doses of hydrocortisone were administered parenterally on an empirical basis together with isonicotinic hydrazide, streptomycin, and chloramphenicol. The patient died unexpectedly five days after corticoids were withdrawn.

Interpretation. The finding of a necrotic lesion partially surrounded by a concentric fibroblastic capsule and of multinucleate giant cells in an adrenal that was only slightly involved is unique among the numerous adrenals examined in connection with this study. It is probable that an adrenal focus existed before the initiation of corticoid therapy but that, with the advent of corticoid-induced pituitary adrenal hypofunction, both cryptococcal proliferation subsided and fibroblastic proliferation and giant cell formation began (FIGURE 13). The adjacent necrotic area containing numerous extracellular cryptococci unaccompanied by fibroblasts (FIGURE 14) represents a recent extension that presumably developed when corticoidogenesis recurred and corticoid levels increased

in the adrenal following withdrawal of corticoid medication. Adrenocortical lipids were preserved in solid sheets, indicating that adrenal function had not resumed to any major degree following cessation of corticoid treatment five days prior to death. The contralateral adrenal was largely infarcted secondary to recent central vein thrombosis.

While, characteristically, the histologic reaction to cryptococci in the meninges is sparse and more or less purely mononuclear, the extensive necrosis of cellular exudate and the fibroblastic proliferation as observed in this case are distinctly unusual (FIGURE 16),[15] as is the character of the recent exudate consisting of giant cells, plasma cells, and lymphocytes. The possibility that this may be a corticoid-induced modification receives support in the finding of a similar reaction in the next patient.

Case 28

Cryptococcosis was treated, in this case, with 100 mg. of cortisone intramuscularly for the last 3 days of life. The patient had complained of fever, headache, vomiting, and diarrhea, unrelieved by penicillin, for 5 weeks.

While her meningeal exudate was distinctly mononuclear in character, pyknosis and considerable fresh nuclear debris were present. This is believed to have developed in result of corticoid administration (FIGURE 15). The absence of such reaction in the kidney presents at least a seeming inconsistency; however, cellular reaction was not pronounced, and multinucleate giant cells did not show nuclear pyknosis and coarse cytoplasmic vacuolization. The adrenal lesions consisted of multiple small foci of intracellular fungi with necrosis of individual cortical cells only (FIGURE 12).

Case 29

This patient with cryptococcosis, who was treated with ACTH, exhibited a generalized pruritic rash of 2 months' duration, with recent periorbital and pedal edema. This followed an attack of pneumonia 5 months previously. The patient was found to have albuminuria (25 gm./l.), numerous red blood cells, and 8 to 10 white blood cells with granular casts in the urinary sediment, and his blood nonprotein nitrogen was 110 mg. per cent. The diagnosis was possible acute glomerulonephritis, and he was treated with repository ACTH for the last 6 weeks of his life.

Although the adrenals were stated to be of "normal" size in the gross, the corticotrophic effect was unmistakable in view of the hypertrophied eosinophilic cortical cells showing large and sometimes multiple nuclei (FIGURE 11). Small foci of cryptococci were present intracellularly or with necrosis, accompanied by a few neutrophils and occasionally by lymphocytes (FIGURE 11). While the liver was involved to a similar

degree, the inflammatory reaction included larger numbers of neutrophils and lymphocytes, in addition to macrophages and giant cells that were not present in the adrenals. The lung showed numerous macrophages containing cryptococci. Subacute glomerulonephritis was present with superimposed interstitial nephritis and glomerulitis due to cryptococci. There was minor cryptococcal involvement of spleen, myocardium, an atheromatous plaque in a coronary artery, and lymph nodes. The central nervous system was not examined.

Interpretation. In contrast to the preceding cases of cryptococcosis, where a sudden reduction of adrenal function was induced by corticoid therapy, the administration of corticotrophin to this patient increased adrenal activity, and this was well documented histologically. The cryptococci were within cortical cells and gave rise to almost purely necrotic lesions. Elsewhere neutrophils predominated, except in the lungs, where the fungi grew in macrophages. In addition, giant cells were found in the liver.

Case 30

This case represents an instance of corticoid-induced relapse of tuberculosis. Pulmonary components of the Ghon lesion were identified, consisting of encapsulated foci of caseation necrosis with acid-fast bacilli. Several hilar lymph nodes were similarly involved. In addition, however, there were recent lesions in liver (FIGURE 7), lymph nodes and spleen, characterized by necrosis, surrounded by a thin rim of immature epithelioid cells and sparse giant cells. Tubercle bacilli, confirmed by culture, were most numerous in the lymph nodes. No adrenal lesions were present, but there was preservation of much lipoid and of birefringence consistent with corticoid-induced pituitary-adrenal hypofunction. This patient was treated with prednisone for a slight leukopenia, which followed a mild respiratory infection. He developed fever. When the medication was stopped, he started to vomit and became stuporous. His blood sodium was 124 mEq., potassium 3.6 mEq., chloride 86 mEq., carbon dioxide 18.5 mEq. per liter, and urea nitrogen 13.3 mg. per cent. Cortisone therapy controlled his symptoms. The patient died with aspiration pneumonia 4 days later.

CASES OF ADRENAL DESTRUCTION REVIEWED AT THE ARMED FORCES INSTITUTE OF PATHOLOGY

Fifty-five cases classified as Addison's disease or necrosis of adrenal were reviewed at the Armed Forces Institute of Pathology. Of these, 26 were unsuitable for this study, such as cases of adrenal atrophy or lesions associated with amyloidosis, meningococcemia, diphtheria, typhoid fever, neoplasms, and central vein thrombosis. Of the remaining

29 cases showing granulomatous inflammation in other organs, 19 showed necrotic adrenals similar to those described here; in 2 the inflammatory reaction in the adrenals was similar to the reactions elsewhere; and 8 cases could not be properly evaluated since either no organisms were found, no extra-adrenal lesions were represented, or corticoids in ill-defined quantities were given at unstated times.

DISCUSSION

Study of 19 cases of tuberculosis, histoplasmosis, and coccidioidomycosis, documented in TABLES 2 and 3, has shown that lesions in the adrenals differ in several respects from extra-adrenal lesions in the same patients. As a rule, the adrenal glands contain more microorganisms, there is a greater tendency for necrosis, the organ as such is more extensively destroyed, and the inflammatory reaction is depressed, as indicated by the decreased number or absence of epithelioid and giant cells and by the lesser degree of fibrosis. These findings were confirmed in 19 of 21 cases of chronic adrenal infection from the Armed Forces Institute of Pathology.

Historical

There have been occasional statements referring to the character of the adrenal necrosis as being different from the "ordinary caseous necrosis of tuberculosis, in that the necrotic process was yellow or yellowish-gray, firm and rubbery and on section presented a uniform surface."[17] Barker further notes that "this gross picture is well known to pathologists as being characteristic of Addison's disease and differing from most tuberculous necrosis found in other parts of the body."[17] He adds, "From observations on suprarenal glands from approximately 1000 necropsies at the Mayo Clinic, small areas of healed tuberculous lesions, such as those which are found in the lungs, liver, and spleen have not been found in the suprarenal gland. Robertson, with a much larger experience in necropsy work, stated that he had never seen evidence of healed tuberculous lesions in the suprarenal glands." When discussing subtotal adrenal destruction in patients with Addison's disease, the histologic appearance of lesions was said to vary between that described above and the more conventional granulomatous response. However, Barker did not correlate the histologic reaction with the presence or absence of functional adrenal cortex in the particular region, nor did he systematically compare lesions in the adrenals with those in the other organs in the same patient.

While the occurrence of adrenal involvement with tuberculosis is rare, being quoted[3] as varying from 2 to 5 per cent in different series, the *extent* of adrenal destruction is often remarkable compared to the paucity

of other lesions in the same patient.[2] Guttmann observed that "in the majority of cases ... the extrasuprarenal lesions are not extensive and are clinically latent."[3] A number of hypotheses have been advanced to explain the occurrence of the extensive and apparently isolated bilateral adrenal necrosis leading to Addison's disease. "Primary tuberculosis," "inheritance or transplacental transmission," "a hypoplastic condition of the chromaffin system which is associated with status lymphaticus," "developmental hypoplasia," or a "predisposition ... as the result of a low fat content of the tissues," on account of "a previous acute infectious disease," or secondary to "allergy" have been quoted by Guttmann[3] in his extensive review article. These hypotheses were briefly discussed and found wanting as over-all explanations.[3] Certain mystical scientific concepts prevalent in the early 1900s and misinterpretation of effects for causes are readily apparent now. The approximately sixtyfold greater frequency of bilateral than unilateral involvement led to Löwenstein's hypothesis[16] that infection of one organ of a pair leads to susceptibility of the other through mediation of organ-specific antibodies ("resorbins"). He cites eyes, kidneys, and adrenals as examples. Preoccupation with the causality principle, with unilateral infection leading to contralateral infection, appears prejudicial toward considering simply that both members of a pair of organs, being similar, may be more highly susceptible as such.

Much of the discussion in the older literature concerns tuberculous etiology, 17 per cent in Guttmann's review, although diagnoses were usually based on clinical consideration and more often than not were undocumented by the finding of acid-fast bacilli. Rarely was syphilis mentioned (0.25 per cent), while fungal infections were as yet largely unrecognized. Their importance in relation to adrenal insufficiency was first emphasized in 1948.[29]

Evidence Linking Adrenal Infection and Necrosis with Endogenous Production of Corticoids

To aid a detailed analysis of the pathogenesis of adrenal infection in man, the experimentally observed features of adrenal infection and their counterparts observed in the human are listed in TABLE 5. Details of differences in adrenal and extra-adrenal lesions are listed in TABLES 2 to 4 and 6.

Do Steroids Act as Substrates for Microbial Metabolism in the Body or Do They Act by Modifying Cellular Reactions?

Certain fungi can hydroxylate the steroid nucleus to the extent that they are useful for *in vitro* synthesis of corticoids.[22,23] However, there

is no evidence that hydroxylation by microbes *in vivo*, as at the 11 or 17 positions of progesterone, results in immunity-depressing corticoids that

TABLE 5

ADRENAL INFECTION AND CORTICOID EFFECTS

*Experimentally observed in hamsters**	*Cases illustrating equivalent lesions in man**
Besnoitia infection	
Progressive adrenal infection and necrosis during period of chronic infection lasting many months, in absence of similar progression in other organs of same animal[6]	Histoplasmosis, cases 1-5, 7-8 Tuberculosis, cases 9-11
Inhibition of progressive adrenal infection and lesions by	
(a) hypophysectomy[6,†]	
(b) pharmacological doses of corticoids sufficient to produce pituitary-adrenal hypofunction[6]	Case 25 (extension of adrenal parasitism prevented) Case 27 (healing of adrenal focus)
(c) chemical inhibitors of steroidogenesis, amphenone and analogues[†]	
Corticoid-induced exacerbations of chronic latent infection[6,8,62]	Case 30 (tuberculosis)
Local corticoid-induced lesions[6]	Case 24 (histoplasmosis)
Primary infection more fulminant[6,63]	Case 26 (histoplasmosis)[33,44,48-50]
Mycobacterial infection[10] (giving rise to complex granulomatous inflammation)	
Organisms more numerous in adrenal lesions than elsewhere	Histoplasmosis, cases 1-8, 25 Tuberculosis, cases 9-11, 15, 17 Cytomegalic virus, case 22 Herpes, case 21
Necrotic adrenal lesions *versus* epithelioid-giant cell reaction in other organs	Histoplasmosis, cases 1-8 Tuberculosis, cases 9-11, 13-17 Coccidioidomycosis, case 18
Corticoid-induced changes in inflammatory reaction (Lurie[9])	Cryptococcosis, cases 27, 28 Tuberculosis, case 30

*In hamsters and man hydrocortisone is the principal adrenal secretory product.[18,19,20]
†Frenkel, unpublished observations.

TABLE 6

RELATIVE DIFFERENCES IN ADRENAL AND OTHER LESIONS

	Extra-adrenal Microorganisms	*Granuloma*	*Necrosis*
Cryptococcosis	++	+	±
Histoplasmosis	+++	++	+
Tuberculosis	+	+++	++
Coccidioidomycosis	++	++++	+
Cytomegalic virus infection	Inclusions +	−	+
	Adrenal		
Cryptococcosis	+++	−	+
Histoplasmosis	++++	−	+++
Tuberculosis	++	+	+++
Coccidioidomycosis	+++	++	++
Cytomegalic virus infection	Inclusions ++	−	++
GENERALIZATION			
	Extra-adrenal		
Eucorticoid	"Standard for specific case"		
	Treatment superimposed on existing lesions		
Corticoid Rx	↑	↓	↑
ACTH Rx	↑	↓	↑
	Adrenal		
Eucorticoid	↑	↓	↑
	Treatment superimposed on existing lesions		
Corticoid Rx	↓	↑	↓
ACTH Rx	↑ or ↓	↓	↑

Quantitative differences in the strength of expression of an entity are indicated by +, ++, +++, ++++; − indicates the absence, and ± the irregular presence of the item listed.

Changes in the expression of entities are indicated by ↑ for an increase and by ↓ for a decrease.

play a role in the pathogenesis of the lesions discussed here. At least the ovaries appear to be generally unaffected and, as discussed, even in the adrenals corticotrophic action is necessary, while microbial hydroxylation *in vitro* does not require ACTH.

That nonsecretory adrenal cortical cells do not provide exceptionally good substrate for utilization by microbes is shown in the cases where there was corticoid-induced adrenal hypofunction. Here, more *Histoplasma* grew in the lymph nodes than in the adrenals (case 26). In hamsters the

adrenals do not ordinarily become infected after hypophysectomy or when ACTH-release-inhibiting doses of corticoids are administered, while many other tissues show extensive parasitization.[6] In certain critical dose ranges the number of necrotic foci in the adrenals varies inversely with the dosage of inhibiting corticoids injected (Frenkel, unpublished observations). The administration of ACTH to hamsters with either type of adrenal hypofunction again results in adrenal involvement. Hence, parasitization of the adrenals is dependent on their endocrine function.

That the corticoids as such are utilized by microbes would appear unlikely. Only the steroids that are anti-inflammatory increase proliferation in tissues (unpublished observations). Therefore, it would be an unusual coincidence if a variety of microbes, including viruses, could utilize natural and substituted corticoids in parallel to their anti-inflammatory activity. Experimentally, the alcohols of progesterone, desoxycorticosterone, corticosterone, hydrocortisone, hexamethasone, and triamcinolone failed to stimulate growth of either *Histoplasma* or *Candida* on blood plates. Indeed, desoxycorticosterone was markedly inhibitory, and some of the others slightly so (unpublished observations).

Natural Resistance and Acquired Immunity as Affected by Corticoids

Perusal of cases in TABLES 2 and 3 will indicate that the disparity of adrenal and extra-adrenal lesions is much more striking in chronic infections than in acute disseminated ones. This difference would appear to be attributable to the more significant quantum of acquired immunity, when compared to natural resistance. Both are reduced to near baseline levels by endogenous corticoids in the adrenals. That a partial immunity exists in chronic infections is manifested by the occurrence of well-developed granulomas, some of which subside with fibrosis in the extra-adrenal organs. The duration of infection would favor the production of more spectacular lesions in chronic infections. Although some dimorphism in lesions can be detected in most acute infections where the adrenals are involved, it may be quite subtle. In newborn babies differences are least marked and sometimes absent. Possibly this is a consequence of the low degree of their natural resistance, with little cellular reaction to be inhibited, and of their low output of corticoids when compared to that of adults.[21]

When the effects of corticoids are studied quantitatively, as in *Besnoitia* infection of hamsters, it is found that they modify acute fatal infection but little, since the host is already near maximally susceptible. With increasingly prolonged infections, where the factors of acquired immunity become progressively more important, resulting in milder lesions, the aggravating effects of corticoids become spectacular (unpublished observations).

Effects of Endogenous Corticoids on the Pathogenesis of Specific Infections

Relatively long-standing generalized *tuberculosis* with partial involvement of the adrenal glands provides a useful point of departure for a study of the variations in lesions observed. The adrenal lesions are predominantly necrotic in character, being separated generally by only a few lymphocytes from viable adrenocortical cells (FIGURE 6). Occasionally a few plasma cells, mononuclears, immature epithelioid cells, or a rare giant cell are found. There is no fibrosis. However, where all cortex is destroyed, the character of the lesion changes to that considered typical of tuberculosis (FIGURE 19) in conformance with the reaction seen in extra-adrenal sites (FIGURE 5). When glucocorticoids are administered in pharmacological doses, the lesions in all the viscera assume a prominently necrotic character, accompanied by but little granulomatous inflammation (FIGURE 7). The number of bacilli is generally greater in areas under the influence of 11-, 17-hydroxylated corticoids, whether exogenous or endogenous. Usually, organisms are seen extracellularly. Both hypersensitivity and microbial qualities appear to play a significant role in producing cell necrosis, even under conditions of corticoid influence.

Histoplasmosis. In this infection, granulomatous inflammatory reaction is generally less proliferative or exudative than in tuberculosis. Hence, lesions in the adrenals may be purely necrotic, with hardly even a lymphocyte in attendance. The degree of intracellular parasitism tolerated is much greater than that seen in tuberculosis. Cellular destruction appears to depend largely on the quantity of intracellular *Histoplasma.*

In visceral lesions, macrophages are prominent. Epithelioid cells with giant cells are especially numerous in those patients with a proclivity toward a sarcoidlike response, in whom also the contrast to the necrotic adrenals is noteworthy. Necrosis may occur also in lymph nodes that support the growth of vast numbers of organisms. Repair by fibrosis may be found in all extra-adrenal sites, but in the adrenals only in areas where all cortical cells have been destroyed. In several cases, anucleate *Histoplasma,* presumably nonviable, were present in large numbers. Wherever both nucleate and anucleate organisms occurred together, the former predominated in the adrenals, the latter in the other organs. In 103 cases of fatal disseminated histoplasmosis, adrenal involvement has been recorded in 35 per cent, with clinical symptoms of adrenal insufficiency in about half of these.[25] In Schulz's review[31] of 112 cases, the incidence of adrenal involvement was 46 per cent. In a group of cases of disseminated histoplasmosis, Binford[30] found adrenal involvement in 21 of 22.

Coccidioidomycosis. In the case studied, this infection gave rise to a granulomatous reaction that is more productive than either of the entities

just discussed. Even in the adrenals, epithelioid cells, although immature, are numerous, as are giant cells; however, fibrosis is absent (FIGURE 8). The alternate expression of the lesions is exemplified in the meninges and in the lungs, where epithelioid cells are mature and fibrosis is well developed, while necrosis is absent (FIGURES 9 and 10). The number of fungi appears to be similar in all organs, although endosporulation was found only in the adrenals, giving rise to minute suppurative foci as described by Forbus and Bestebreurtje.[24] In their monograph on coccidioidomycosis, subtotal adrenal destruction was found in 16 of 50 cases studied at autopsy.

Blastomycosis. Adrenal involvement results from this infection more rarely. However, a number of cases have been reported[26,27] where the adrenals showed a significant necrosis. In two cases of South American blastomycosis due to *Blastomyces (Paracoccidioides) brasiliensis*, the necrotic reaction in the adrenal glands, resulting in subtotal destruction, was contrasted with more proliferative granulomatous lesions, present in other organs.[28]

Cryptococcosis. This infection of the adrenals has been described but rarely. However, 8 cases with adrenal involvement have been collected by Rawson *et al.*,[29] 1 has been described by Rigdon and Kirksey,[32] 3 by Baker and Haugen,[45] and 2 others are mentioned by Littman and Zimmerman.[15] The small foci observed in cases 28 and 29 appear to represent the commonest pattern of adrenal involvement, but massive necrosis also has been observed.[29,32,45] Although case 28 was treated with cortisone for 3 days, it is not believed that the character of adrenal lesions had changed significantly, as was postulated for the meningeal exudate. In case 29, treated with ACTH only, the exclusively intracellular parasitism in the adrenal should be emphasized. In liver, lung, and spleen extracellular organisms were common, and macrophages, giant cells, and fibrosis were present beyond the meager lymphocytic and polymorphonuclear reaction focally present in the adrenals. The degree of organ involvement was greater in lungs and kidneys, suggesting that the establishment of adrenal foci may be more difficult although, once involved, the number of organisms produced tended to be greater.

Viral infections. Adrenals affected by these infections appear to be rare (this might indicate that the adrenal cortex proves relatively inaccessible to viruses, provides a poor substrate, or is relatively invulnerable). Individual factors may be attributable to either "natural resistance" or to "acquired immunity." The relative effectiveness of antibody in viral immunity (demonstrable by passive transfer) and the readiness with which antibodies to viral infections are generally elaborated may, in some instances, prevent involvement of the adrenal glands. Alternately, the frequency of fatal generalized viral infections in the neonatal period may

result, in part, from the suboptimal capacity to develop antibody. The examples of herpes simplex and of varicella listed in TABLE 3 were from infants.[33,34]

The recognition of viral growth is limited essentially to the finding of inclusions or other evidence of drastic cytopathology. Involved cells may occur singly, they may then lyse, being lost for observation, or they may remain to form areas of necrosis. Such was the case in the nine-month-old child with herpes (case 21), where the adrenals yielded highest viral titers of any organ.[14] In cytomegalic infections of adults, case 22, and in others,[35-37, 55-57] viral inclusions were of widespread occurrence only in the adrenals. Extensive bilateral necrosis was considered the immediate cause of death in Amromin's case.[56] Hence, while corticoids apparently enhance adrenal involvement with certain viral infections, Addison's disease following a viral infection appears to be rare. The focal adrenal involvement with cell to cell extension, as in case 22, indicates that important inhibitory (immune?) factors remain active.

Differences in inflammatory reaction between adrenal and extra-adrenal lesions are subtle in the absence of a granuloma.

Idiopathic adrenal atrophy. While adrenal "atrophy" or "contraction"[38] is of unknown etiology, the possibility that endogenous corticoids predispose to it should be considered. Friedman,[38] in his comprehensive discussion, concludes that these lesions "bear a strong resemblance to the lesions of necrotizing hepatic injury and its sequelae." While adrenal necrosis is not associated with viral hepatitis, the possibility exists that other viruses might localize in adrenals, giving rise to cytolysis followed by quick removal of cellular remnants and stromal collapse, but little scarring. In cytomegalic infection, cellular debris remains in the adrenals. Toxic chemicals, such as dichloro-diphenyl-dichloroethane (DDD) and certain analogues have been observed to give rise to "contraction" of adrenal fasciculata and reticularis in dogs.[39] One of its analogues, effective in rats, was found to be inactive in hypophysectomized rats (J. Nichold, personal communication).

Adrenal hemorrhage and "pseudotubular degeneration." Lesions resulting from meningococcemia,[46] endotoxin, exotoxin, or ACTH deserve brief consideration as unique to the adrenal gland. Tonutti's investigations,[40] summarized in English,[41] indicate that a functional adrenal is necessary to reproduce pseudotubular and hemorrhagic lesion in guinea pigs injected with diphtheria toxin. Hypophysectomy abolishes the lesions, and the injection of ACTH again permits their expression. Since the intracutaneous injection of corticoids does not sensitize to local toxin action, the lesions appear to be peculiar to adrenal cells under the influence of ACTH, possibly of one of its noncorticoidogenic attributes.[51] Wilbur and Rich[42] showed that cytolysis resulting in pseudotubular degeneration can

be produced by the injection of large doses of ACTH in rats. Hemorrhagic necrosis has been attributed in part to direct cytotoxicity, demonstrable with some endotoxins even in hypophysectomized animals.[41]

The occurrence of fibrin thrombi and of hemorrhagic necrosis in adrenals of patients with meningococcemia and in the glomeruli of rabbits with the generalized Shwartzman phenomenon suggests a relationship. Thomas and Good[43] have shown that the local and generalized Shwartzman reaction can be elicited in cortisone-treated rabbits without a preparatory injection of endotoxin. This suggests interpreting the hemorrhagic adrenal necrosis as a Shwartzman phenomenon, localized to the adrenals since they are actively corticoidogenic. Treatment of such patients with pharmacological doses of corticoids could precipitate a generalized Shwartzman reaction, possibly accompanied by renal cortical necrosis as seen in rabbits. Margaretten and McAdams[59] have recently equated all the hemorrhagic phenomena of meningococcemia with the Shwartzman reaction. Their theory comprises the views expressed above.

Effects of exogenous corticoids on chronic infection. Pharmacological effects from corticoids may be apparent from the activation or spread of infection, from the change in the character of inflammatory reaction, and from the atrophy of the adrenals. Local activation of infection by ingested cortisone would appear to explain the intensive involvement of Peyer's patches and mesenteric lymph nodes with *Histoplasma* in case 24, whereas involvement of other, distant lymph nodes is minimal. Generalized activation, especially in the highly susceptible lymph nodes, with spread to liver and spleen, followed 19 days of prednisone therapy for leukopenia in a patient with healed primary tuberculosis of the lungs (case 30).

Inflammatory cells sensitive to corticoids are destroyed, as shown by the pyknotic and necrotic mononuclear cells in the meninges of case 28 (cryptococcosis), treated with 100 mg. of cortisone for 3 days prior to death. An atypical inflammatory reaction resulted after long-term treatment in case 27; surrounding the necrotic exudate, which still contains cryptococci, is a zone of fibroblasts and giant cells, with plasma cells, and small lymphocytes peripherally. Thin, fibroblastlike immature epithelioid cells and a few giant cells surround foci of incomplete necrosis with large numbers of tubercle bacilli in the lymph nodes of case 30.

Corticoid-induced pituitary-adrenal hypofunction may deprive organisms, parasitic in the adrenals, of their privileged sanctuary, and can result in healing with fibroblastic proliferation and slight collagen deposition around a focus of adrenal necrosis, as in case 27. This accidental clinical experiment, duplicating experience with chronic *Besnoitia* infection in hamsters treated with corticoids, provides probably the first described example of a healing lesion due to either fungi or tubercle bacilli in the adrenals. Attempts were made to achieve healing in case 25

by the administration of large doses of corticosterone. Although the patient died prematurely, there was evidence of cessation of histoplasmic proliferation in the small amount of regenerated cortex, while large numbers of ghost forms of *Histoplasma* filled all the necrotic adrenal cortex (FIGURE 4). A hypofunctional adrenal cortex presumably explains why, in case 30, the adrenal is not involved with tubercles.

An acute infection superimposed on corticoid therapy is liable to be more extensive and prolonged.[47-50,58] Case 26 is an example of progressive histoplasmosis, exhibiting extreme numbers of organisms, leading to necrosis in liver, bone marrow, and lymph nodes. The adrenals, although involved, appear to be poorer substrates for *Histoplasma* under these circumstances of markedly deficient immunity and absence of adrenal hypercorticoidism.

Effects of exogenous corticotrophin. Data are meager on this subject. Only one case of cryptococcosis (case 29), treated with ACTH, was available for study. From the occurrence of fungi in the liver and the degree of pulmonary and renal involvement, one might reasonably conclude that this infection was more extensive than the average fatal case. In addition, the parasitized adrenal cells contained larger numbers of small fungi (FIGURES 11 and 12). ACTH treatment had resulted in cellular hypertrophy without frank hyperplasia.

Experiments in hamsters infected with *Besnoitia* indicated that ACTH accentuates the generalized infection and results in earlier death. However, this is accompanied by a reduction in the number of foci of adrenal necrosis.[6] This finding was unexpected, since a variety of stresses superimposed on *Besnoitia* infection increased the number of foci of adrenal necrosis. That the long-acting gelatin or zinc-ACTH preparations used were active was indicated by their effects on adrenal weight and by the identification of hydrocortisone in the adrenal vein blood of ACTH-treated hypophysectomized hamsters (unpublished observations). Activity was also indicated by the fact that the adrenals of such hamsters became parasitized with *Besnoitia*, especially when adrenal hypertrophy-inducing doses of ACTH were administered (unpublished observations). Since heterologous (porcine) corticotrophin is used in both hamster and man, difference in action of endogenous and exogenous ACTH need be considered. These may be due to changes in type and amounts of corticoids produced, or to the rate of storage or excretion. Alternately, the presence in porcine ACTH (vis à vis the hamster adrenal) of an undue amount of "adrenal weight factor" could falsely suggest high corticoidogenic activity, while suppression of endogenous ACTH accounts for the decrease in adrenal necrosis. Extra-adrenal effects of ACTH, especially from a foreign species, could modify adrenal infection in directions as yet unsuspected.[51]

One might conclude that exogenous ACTH in man might accentuate generalized infection and might lead to potentiation of adrenal parasitism, but not necessarily to the degree expected from the endogenous hormone under endogenous homeostatic control.

Therapeutic Implications Concerning the Pathogenesis of Adrenal Infection

If one accepts the determinant role of endogenous corticoid in producing an immune deficit, permissive of chronic progressive adrenal infection, the latter might logically be treated by inhibiting the local production of hydrocortisone, thereby raising effective tissue immunity. This has been shown to be feasible in experimental *Besnoitia* infection of hamsters.[6] Its use has been discussed in connection with cases 25 and 27. All the glucocorticoids used for substitution therapy are effective in inhibiting ACTH-release and consequently inhibit corticoidogenesis. However, since hydrocortisone, triamcinolone and, presumably, other glucocorticoids are immunity-depressing in doses necessary to suppress ACTH and adrenal necrosis, search for an ACTH-inhibiting steroid with less immunity-depressing activity appeared indicated. Of a number of compounds tested, corticosterone, 11-beta OH-progesterone and 6-methyl-17-acetoxyprogesterone showed the most favorable ratios(Frenkel,[6,62] and unpublished observations).

Desoxycorticosterone, the trimethyl acetate, shows little immunity-depressing effect. Hence this mineralocorticoid is useful to reduce the amounts of exogenous corticoids required for replacement. Of the other salt retainers 2-methyl, 9-alpha fluorohydrocortisone was shown to have a useful mineralocorticoid/immunity depressing ratio, but other 9-fluorinated compounds tested did not.[62]

Certain amphenone derivatives, especially 2-methyl-1,2-bis-(3-pyridyl)-1-propanone*, show great promise as inhibitors of 11-hydroxylation,[60] from which results the basic immunity-depressing activity. This leads to a shift in major adrenal output from hydrocortisone to 11-desoxy-17-hydroxycorticosterone (Reichstein's cpd. S) and to 11-desoxycorticosterone (DOC), both of which regulate mineral metabolism, and would appear to be tolerable compromises for "life maintenance."

Avoidance of hyperglucocorticoidism is of little importance in those cases that can be treated effectively with bacteriostatic and fungostatic chemotherapeutic agents. Hence, tuberculosis and histoplasmosis should should be controllable by chemotherapy alone. Case 8 (TABLE 2) is a good example of the efficacy of amphotericin-B in histoplasmosis of the adrenal glands. Endocrine control of adrenal infection would appear to be

*SU-4885, CIBA Pharmaceutical Products Inc., Summit, N. J.

helpful in virus infections, such as with the cytomegalic agent, herpes, and in those instances where the etiologic agent is unknown and no logical antimicrobial treatment is possible.

Microbe, Intracellular Substrate, Corticoids, and Host Immunity in Determining Preferred Tissue Parasitization

As expressed by the variety of lesions observed, many factors determine host-microbial interactions. A number of microorganisms appear to grow better in one tissue than in another, suggesting more effective utilization of organ-specific substrates. Throughout this study it was apparent that tubercle bacilli multiplied better in lymphoid than in other tissues, including the adrenals. The latter became foremost centers of proliferation only after a high degree of immunity had been achieved elsewhere. Adrenal lesions appeared to be caused with greater frequency in disseminated histoplasmosis than in military tuberculosis. *Histoplasma* was present intracellularly in large numbers, both in adrenocortical and sinusoidal lining cells. Tubercle bacilli were found extracellularly and sparsely, suggesting either extracellular growth or early disintegration of infected cells with liberation of bacilli.

Cell necrosis was prominent in lymph nodes during early infection and in the adrenals later, if they became involved. Tubercle bacilli are more numerous in the lymph nodes during early infection than in the adrenals later. *Histoplasma* may be similarly numerous in either location. If corticoids depress immunity to a similar degree in these two infections, then the adrenals appear to be a better substrate for *Histoplasma* than for tubercle bacilli.

Necrosis results from microbial proliferation and from secondary hypersensitivity. Both need to be evaluated. Since adrenal corticoids depress both hypersensitivity and acquired immunity, the proliferation resulting from depression of the latter appears of greater importance in causing cell death. This is borne out by the finding of relatively large numbers of organisms associated with necrotic lesions in the adrenals.

The dimorphism in cellular response occurs even where similar numbers of organisms are present; although an epithelioid-giant cell-fibrosing reaction or a "sarcoid" type of response may be present throughout other organs, necrosis predominates in the adrenals.

The occurrence of adrenal infection is a result of several circumstances: (1) immunity must be acquired with sufficient speed to prevent death from overwhelming generalized infection or from lesions in "vital" organs (such as the brain, another area where resistance and immune mechanisms are less effective); (2) the organisms must reach the adrenals

and be able to utilize adrenal substrates; (3) key mechanisms that maintain acquired immunity must be reversible by endogenous corticoids (hydrocortisone); (4) the degree of acquired immunity must be marginal, permitting organisms to persist; and (5) the amount of hydrocortisone present in the adrenals under near-physiological conditions must be sufficient to negate this immunity. The second condition probably indicates why more organisms do not give rise to progressive adrenal lesions. The third condition concerns the corticoid sensitivity of the immunity to specific infections. The fourth condition explains the low incidence of adrenal lesions in those infections where it does occur.

The immune mechanisms influenced by endogenous corticoids appear to be largely cellular and relatively independent of antibody mechanisms. This statement is accepted, readily, perhaps for tuberculosis and the fungus infections that more commonly are the cause of adrenal necrosis. The apparent interference of antibody with viremia may in part prevent viral spread to the adrenals. However, the ease of measuring antibodies to viral infections and their usefulness in retrospective diagnosis has tended to overemphasize the importance of antibody in immunity to infections as a whole. Pharmacological levels of corticoids can only delay the primary and anamnestic synthesis of such antibody, whereas existing antibody levels are not significantly impaired.[48-50]

The almost regular acquisition of solid immunity to viral infection in agammaglobulinemic patients indicates the presence of nonantibody immunity, generally believed to be cellular. This had previously been shown for immunity against tuberculosis.[9] In certain infections this immunity is antagonized qualitatively by corticoids in parallel with their anti-inflammatory activity.[6] Such active corticoids employed in the pharmacological range depress seemingly "solid," acquired immunity in a semi-quantitative manner.[62,63] The intracellular habitat of the microorganisms and the need for phagocytosis *and digestion* for effective immunity indicate the importance of cellular immunity in these infections. The apparent predominance of cell to cell spread and the absence of hematogenous dissemination in the stage of infection when adrenal necrosis evolves would indicate that antibody mechanisms, if present, remain effective.

Summary

It has been shown that endogenous adrenal corticoids are permissive of the progressive microbial growth that results in adrenal necrosis terminating in Addison's disease. In hamsters where, as in man, the principal corticoid is hydrocortisone, the selective multiplication in the adrenal of *Besnoitia jellisoni* is directly related to adrenal functional activity. Multiplication was inhibited by surgical hypophysectomy or by corticoid-

induced pituitary-adrenal hypofunction. The administration of exogenous ACTH again resulted in progressive adrenal parasitization with this obligate intracellular protozoan.

In man the dependence on corticoid mechanisms has been indicated for adrenal necrosis resulting from tuberculosis, histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, cytomegalic virus infection, herpes simplex and, probably, varicella. While the adrenal hemorrhage of the Waterhouse-Friderichsen syndrome is not related primarily to adrenal parasitization with meningococci, the participation of corticoids in the adrenal lesions, which resemble a Shwartzman reaction, is probable. No evidence bearing on the etiology of adrenal atrophy has been uncovered.

The general level of immunity is depressed locally in the adrenals by the high level of endogenous corticoids present. This results in increased microbial proliferation and more cell necrosis. There is no evidence that corticoids serve as substrates for microbial metabolism.

Specific inflammatory reaction is also moderated by the high level of corticoids. The degree and maturity of epithelioid reaction, giant cell formation and of fibrosis is decreased in the adrenals when compared to lesions in other organs of the same patients. In histoplasmosis and, occasionally, in tuberculosis, there may be *no* granulomatous reaction accompanying adrenal necrosis. In coccidioidomycosis, epithelioid cells are immature and fibrosis is absent in the adrenals, whereas the fully developed granulomatous reaction is present in lungs and meninges. The granulomatous inflammation surrounding a lobe of adrenal completely destroyed by necrosis is characteristic of that present in extra-adrenal tissue. In viral infections, differences between adrenal and extra-adrenal inflammatory reaction lesions are minor.

Selective involvement of the adrenal glands, often with subtotal destruction, is prominent in chronic rather than in acute infections. Frequently there is regression of lesions indicative of healing in many organs and evidence of a defect in acquired immunity only in the adrenals. The dimorphism of lesions was more marked during chronic infection.

Exogenous hypercorticoidism, inducing pituitary-adrenal hypofunction, results in amelioration of the adrenal infection and in recurrence of a local inflammatory reaction. Extra-adrenal lesions generally show a number of organisms greater than expected and a relatively abortive granulomatous reaction. This is also true of infections superimposed on treatment with pharmacological amounts of glucocorticoids.

Administration of corticotrophin (ACTH) appears to accentuate adrenal infection and necrosis and to decrease granulomatous reaction. Extra-adrenal proliferation of microorganisms appears to be accentuated. However, available human data are inadequate, and atypical reactions to heterologous (porcine) ACTH have been observed in hamsters.

Corticoid replacement in patients with active adrenal infection should include desoxycorticosterone to decrease the total corticoid requirements. Certain modified corticoids hold promise for a glucocorticoid/immunity-depressing activity ratio that is greater than that of hydrocortisone. The use of adrenal or ACTH inhibitors to depress corticoid-related adrenal infection has been discussed. With the superiority of specific antifungal and antituberculous chemotherapy, hormonal or chemical control of adrenal susceptibility should be useful mainly when the etiology of adrenal destruction is unknown. Such therapy could allow survival of cortical remnants as nidi for future regeneration.

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